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Antidepressant Use in Children and Adolescents

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No official support or endorsement by the U.S. Food and Drug Administration is intended or should be inferred.

"The Food and Drug Administration (FDA) decision to place a black box warning on antidepressants has precipitated a crisis in the provision of mental health care to children and adolescents."

-Rachel Z. Ritvo, M.D., AACAP News, Jan/Feb 2005

Unknown Consequences of Risk Management Actions?

- What can this experience tell us about implementing risk minimization action plans?
- To attempt an answer we'll consider the following
  - Existing data on antidepressants and suicidal behaviors in pediatric patients
  - FDA Risk management actions
  - Risk management actions by other countries
  - Reactions by stakeholders

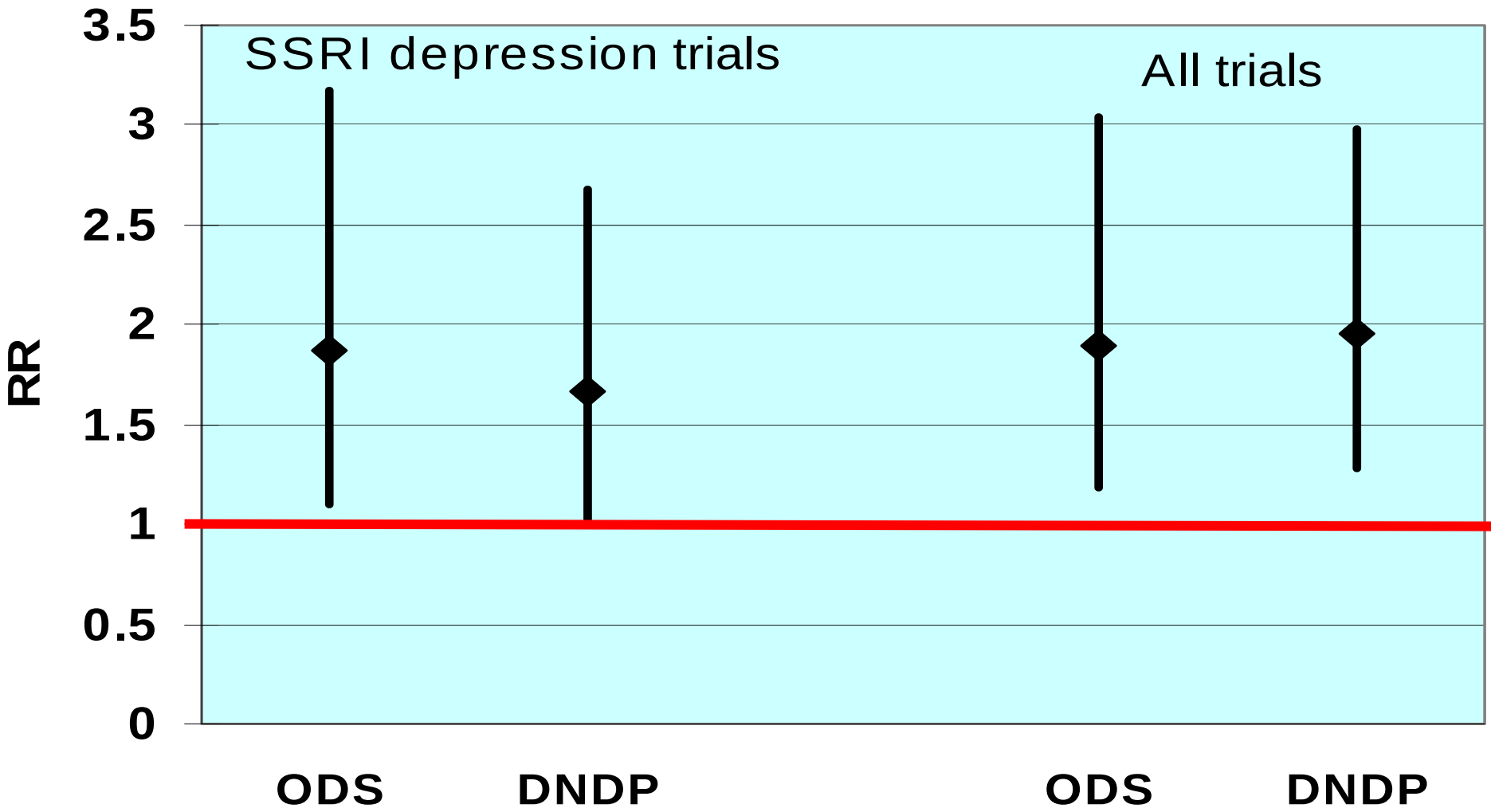
Overview of Available Data on Pediatric Use of Antidepressants

Pediatric Clinical Trial Data Regarding Suicidal Events with Antidepressants

- Two meta-analyses of ~20 randomized, short-term placebo-controlled trials (total n~4200)
  - Office of Drug Safety (ODS)
  - Division of Neuropharmacological Drug Products (DNDP)
- No completed suicides
- Suicide attempts and ideation identified with two different ascertainment methods
  - ODS analysis: primarily automated search
  - DNDP analysis: hands-on adjudication of cases
- Different analytic methods

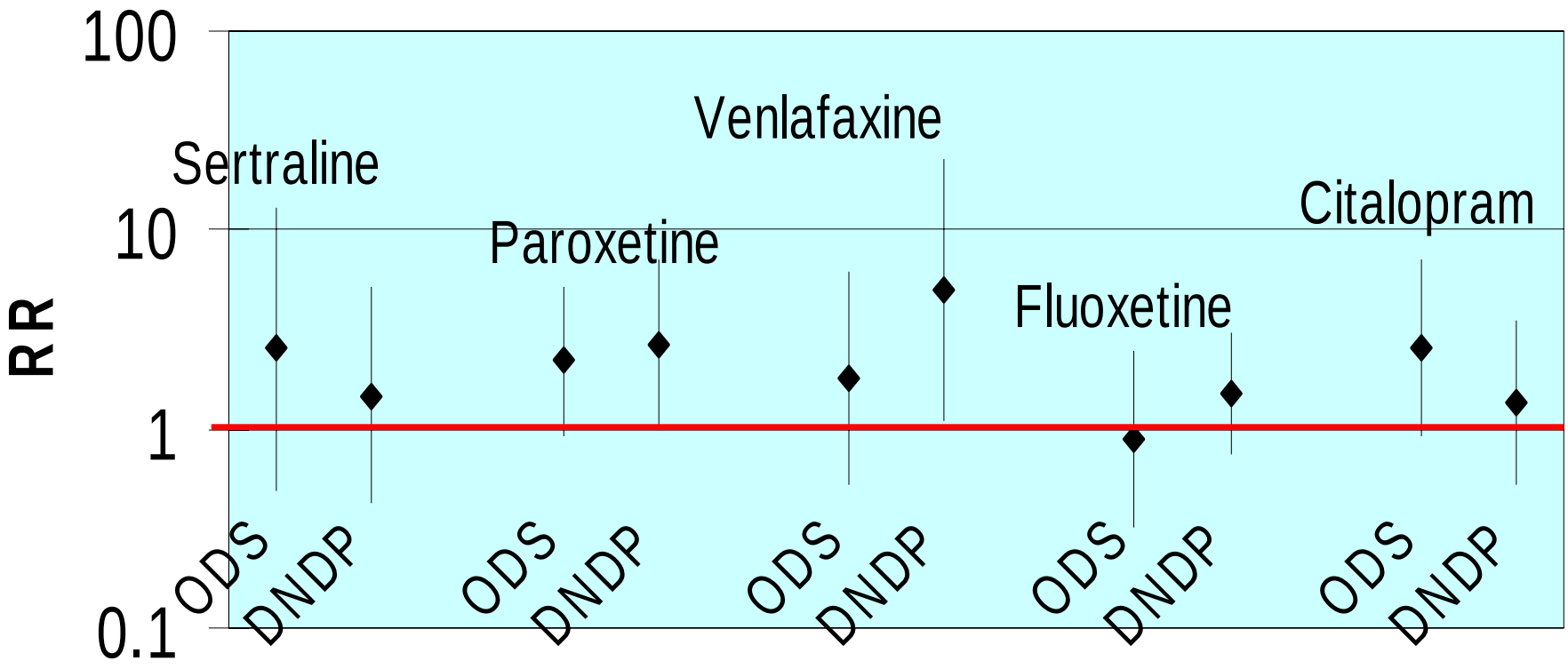
Suicidality Outcomes by Trial Category

ODS and DNDP Analyses of RRs in Pediatric Clinical Trials (with 95% CIs)



Suicidality Outcomes for Selected Drugs

ODS and DNDP Analyses of RRs in Pediatric Clinical Trials with 95% CIs



Meta-analyses: Conclusions

- Both analyses indicate an association of suicidal adverse events with antidepressant drug treatment in short-term, placebo-controlled pediatric trials
- Data are consistent with (but do not prove) a class effect

Ecological Analyses

- Decrease in U.S. adolescent suicide rate has coincided with increased pediatric use of antidepressants
- U.S. 1990-2000: ↑ 1% in antidepressant prescriptions for ≤18 years old → ↓ 0.23 suicides/100,000 per yr
  - Olfson et al. Arch Gen Psychiatry 60:978-82, 2003
- Australia 1991-2000: similar relationship observed for older age groups with higher antidepressant use, but not in 15-24 year olds
  - Hall et al., BMJ 2003;326:1008
- UK 1991-98: increases in antidepressant prescribing for 12-29 year olds not accompanied by drop in suicide rates, although male rate has stopped rising
  - Gunnell and Ashby BMJ 2004;329:34–8

Ecological Analyses

"It is therefore challenging to distinguish the discrete effects of increased antidepressant prescribing from changes in other risk factors."

Gunnell and Ashby BMJ 2004

Pediatric Efficacy of Antidepressants

- Approved in U.S. for pediatric depression:
  - fluoxetine
- Approved in U.S. for pediatric obsessive-compulsive disorder:
  - fluoxetine, sertraline, fluvoxamine
- Clinical trial results for pediatric depression:
  - Fluoxetine: 3 out of 3 trials positive
  - All other antidepressants combined: 1 out of 13 trials positive

FDA Actions Regarding Pediatric Antidepressant Use

FDA Announcement October 15, 2004

- "We are announcing four actions today:
  - First, we are issuing a public health advisory about this increased risk for children taking antidepressants
  - Second, we are informing all manufacturers of antidepressants that we want "boxed warnings" in the labeling of their products.
  - Third, we are also informing these companies that we will require a Medication Guide, or "Medguide" to be distributed with each prescription of an antidepressant.
  - Last, we are announcing that we will work with manufacturers to make these drugs available in "unit-of-use" packaging, sealed and labeled for one course of treatment.
    - Dr. Lester M. Crawford, Acting Commissioner of Food and Drugs, 10-15-2005

FDA Announcement October 15, 2004

- "Based on these data, FDA is asking that the following points be included in the boxed warning:
  - Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
  - Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
  - Families and caregivers should also be advised to closely observe the patient and communicate with the prescriber.
  - Among the antidepressants, only Prozac is approved for use in treating MDD in pediatric patients. Prozac, Zoloft, Luvox, and Anafranil are approved for OCD in pediatric patients. None of the drugs is approved for other psychiatric indications in children."

How Should the Risk Be Described in the Warning?

- All of the following describe the same dataset:
  - Drug treatment doubled risk of suicidal events versus placebo (Relative risk = 2)
  - Drug treatment resulted in a suicidal event for 1 in 50 patients
  - Incidence of suicidal events: Drug 4%; Placebo 2%
  - Roughly 1 excess suicidal event per 9 patient-years of drug treatment for depression

Which Drugs to Include in the Warning?

- "These labeling changes are applicable to the entire category of antidepressant medications because the currently available data are not adequate to exclude any single medication from the increased risk of suicidality."
  - FDA Public Health Advisory 10-15-04

- Tricyclic antidepressants (TCAs) not proven effective in pediatric depression, more toxic than SSRIs. Exempting TCAs from warning could have undesirable consequence of encouraging their pediatric use.
- However: A subsequent case control study found self-harm increased with SSRI treatment of pediatric depression relative to treatment with TCAs.
  - Martinez et al. BMJ 330:389-93, 2005

Actions by Other Regulatory Agencies

Medicines and Healthcare products Regulatory Agency (U.K.)

- "Only fluoxetine (Prozac) was shown in clinical trials to have a positive balance of risks and benefits for the treatment of depressive illness in under 18's."
- "For depressive illness, paroxetine, venlafaxine, sertraline, escitalopram and citalopram are contraindicated. Contraindication means that a medicine should not be used but not that it cannot be used."
  - MHRA press release 12-10-2003

European Medicines Agency (April 2005)

- "suicide-related behaviour…and hostility…were more frequently observed in clinical trials among children and adolescents treated with these antidepressants compared to those treated with placebo."
- "…these products should not be used in children and adolescents except in their approved indications." (No antidepressant is licensed Europe-wide for pediatric depression.)

http://www.emea.eu.int/pdfs/human/press/pr/12891805en.pdf

Reactions by Stakeholders

Regarding the Boxed Warning

- "Pediatricians support stronger warnings, including the black box, as we now know there is definitely an increased risk of suicidal thinking and behavior in children who are on these drugs. The labels needed to change."
  - Carol Berkowitz, MD, FAAP, President, American Academy of Pediatrics, 10-15-04

- "We restate our continued deep concern that a 'black box' warning on antidepressants may have a chilling effect on appropriate prescribing for patients."
  - American Psychiatric Association statement, 10-16-04

Regarding Revisions to FDA Proposed Labeling

[Lenzer BMJ March 19, 2005]

Main revisions:

- October 2004 draft: “Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.”
- Final text: “Antidepressants increased the risk of suicidal thinking and behavior in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.”

- “This is clearly an important change…the FDA warning [is] closer to the actual science.”
  - Dr. David Fassler, APA
- “ This is a very unfortunate weakening of the warning.”
  - Dr. Joseph Glenmullen, Harvard University

Regarding the Decrease in Pediatric Antidepressant Prescribing

- Medco pharmacy benefit manager data showed an 18% decrease in number of pediatric patients on antidepressants for the first quarter of 2004
  - Medco Health Solutions news release, 9-21-04 <www.medco.com>
- "If I would have known how sharply prescription rates were falling, I would not have voted in favor of the black box warning. I hoped the FDA could help to inform patients, but it seems many parents have simply become fearful of anti-depressants..."
  - Gail Griffith, FDA Pediatric Advisory Committee Member
- "You would hope that the inappropriate use of these medicines has dried up a bit."
  - Dr. Richard Malone, FDA Pediatric Advisory Committee Member (NY Times 9-21-04)

Should There Have Been an Informed Consent?

- "…I am curious about the FDA's rationale for not requiring physicians who prescribe these antidepressant drugs to children to provide a clear, informed consent document that parents or guardians must read, understand and sign before accepting a prescription from their physician, as the FDA did for Lotronex."
  - Senator Charles E. Grassley (R-Iowa) 9-17-04

- "…an informed consent process must be established so that the risks are explained to parents BEFORE they are issued a prescription--NOT an after the fact Medication Guide."
  - Vera Sharav, Alliance for Human Research Protection 9-16-04

"[Incoming APA president Steve] Sharfstein, citing a decrease in adolescent suicide rates since the 1990s as antidepressants became more widely used, said he was worried the warning would lead psychiatrists and general practitioners to stop using the drugs, 'and the suicide rate is going to start creeping up.'"

– Philadelphia Inquirer 10-16-2004

"…the current evidence does not suggest that these medications increase the risk of suicide…. these medications may increase the likelihood that a patient will actually tell someone about their suicidal thoughts or even about a suicide attempt. From my perspective, as a child and adolescent psychiatrist, this is actually a good thing…"

-Dr. David Fassler, APA and AACAP representative, testimony before Senate Committee on Health, Education, Labor and Pensions, 3-1-05

Conclusions

- Interpretations of the same data can vary considerably among stakeholders
- Interpretations of the same data can vary considerably among different regulatory agencies
- Interpretations may be impacted by clinical services available in healthcare system
- Many challenges involved in formatting clinical data for risk communication purposes

Selected References

- FDA web site: Antidepressant Use in Children, Adolescents, and Adults

  http://www.fda.gov/cder/drug/antidepressants/default.htm

- September 2004 FDA Advisory Committee Meeting

  Main page

  http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs

  Written reports

  http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf
  http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-11-TAB09a-Mosholder-review.pdf
  http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-12-TAB-9b-Final.pdf

  Slide presentations

  http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065s1.htm

- American Psychiatric Association and American Academy of Pediatrics website regardging antidepressants

  www.parentsmedguide.org